

### REMARKS

Upon entry of the amendments herein, claims 1-25 and 28 remain pending in the application. Claims 1, 9, 13, 14, 16, 18, 19, 21-24 and 28 have been amended. No new matter has been introduced by any of these amendments.

#### I. Objection on the Basis of an Informality

The disclosure has been objected to for an informality on page 17, lines 13 and 14. By amendment herein, Applicants have addressed this matter. The specification has also been amended in several other places in the interest of correcting inadvertent errors and in the interest of clarity.

#### II. Withdrawn Rejection under 35 U.S.C. §101 (Nonstatutory Invention)

Applicants acknowledge with gratitude the Examiner's withdrawal of the previous rejection under 35 U.S.C. §101. On the other hand, as Applicants have noted, the Examiner has stated that the very language said to overcome the §101 rejection is also considered to be new matter. The Examiner advises that removing the alleged new matter "may result in reinstatement of this [§101] rejection." Applicants further clarify in Section III below what is meant by "representing," and this rejection remains moot.

#### III. Rejections under 35 U.S.C. §112, First Paragraph (New Matter)

The Examiner has singled out step (d) of claim 1, **identifying** a set of stacks, based on their evaluated designability, that have **no known counterparts**; and step (e), **representing** backbone configurations comprising the identified stacks. The Examiner asserts that support for steps (d) and (e) is not provided in the specification as filed.

With regard to the issue with step (d), Applicants note in the first place that the Examiner has acknowledged that the specification provides support for sets of stacks that have no **natural**

counterparts. The very language cited by the Examiner provides instruction as to what is intended by the term "known." Applicants happened to use the term "natural" in the cited passage, but could just as easily have used "known" instead. One would not have to be above the ordinary level of skill in the art in this area to understand that "natural" is defined by what has been found in, and is known from, nature. Furthermore, identifying natural counterparts for a highly designable configuration would be straightforward for one of the skill in the art. Several on-line database search tools, including DALI, were available at the time to search among known backbone configurations for counterparts of an input backbone configuration. As such, the means for determining if natural/known counterparts existed for the highly designable stacks obtained in step (c) are, and were, available. In other words, the disclosure of the instant specification and the knowledge in the field at the time of filing provided ample support for step (d) of instant claim 1. Applicants note that the Examiner herself has acknowledged that "if a protein or peptide configuration can be found in the PDB or other prior art, one skilled in the art would consider it to be 'known.'" There is thus basis for the "no known counterpart" component of step (d).

Furthermore, there certainly is basis for the "identification" component of step (d) in the disclosure of the instant specification. In the example, particularly in the description of Figure 3 on page 23, lines 3-12 of the specification, reference is made to a structural comparison of highly designable stacks with natural structures. The identified designable stacks were found to fall within one of four categories of folds, ranked from most to least designable: 1) an up-and-down four-helix bundle; 2) a structure similar to the first, a variant of the up-and-down fold having a crossover connection (i.e., there is a different order of helices along the protein chain); 3) a lambda-represser-type fold; and 4) an orthogonal array. The last of these had never been

observed in nature as the complete fold of a single protein chain. The DALI server was the database used in the comparison of the orthogonal array (part (d) of Fig. 3) to determine its relationship to known and unknown counterparts. The instant disclosure does provide support for the "identifying" portion of step (d) of claim 1.

The Examiner asserts that it is not clear that the designability calculation of step (c) is the same or inherently includes an identification step and goes on to assert that no such step is disclosed anywhere in the specification. The Examiner goes on to cite page 22, lines 6-16 as providing a teaching which is "the opposite of the claimed limitations," i.e., that the cited disclosure is actually a way of identifying stacks which do have counterparts to natural structures. Applicants do not see how this provides any justification for the rejection.

The disclosure cited by the Examiner establishes that the claimed method can in fact result in the generation of stacks that have counterparts among natural folds, thus providing credibility to the method in general as a means of generating stacks that could possibly have some relevance to, and utility in, the "real world." This disclosure does not, as the Examiner would have it, contradict the claimed invention. It must follow that if one can identify generated stacks as having known counterparts, then one can certainly identify the remaining stacks as ones that have no known counterparts. Again, a demonstration of this can be seen in part (d) of Figure 3 of the instant specification. It is further noted that the Examiner herself refers to the concept of comparison of stacks to known counterparts so that stacks without known counterparts may be identified. Thus, regardless of what page 22, lines 6-16 of the specification discloses and as the Examiner has essentially acknowledged, identification of stacks with no known counterparts is the logical and inevitable result of comparing the stacks in question to those counterparts that have previously been identified and are known.

Step (d) of claim 1 has been amended herein to make it clearer that the generated stacks are identified as highly designable and having no known counterparts. The criteria for determining designability are amply set forth in the specification, in general terms on page 6, lines 6-11 and in detail in the passage from page 6, line 12 to the end of page 17. Furthermore, it is recited in claim 1 that the configurations according to the instant invention are "novel in the spatial arrangement and/or connectivity of their secondary structural elements." Accordingly, step (d) of claim 1 cannot be said to constitute new matter.

Similarly, one cannot consider that the addition of step (e) to claim 1 constitutes new matter. This addition was made by amendment in Applicants' previous response to be responsive to the Examiner's concerns. However, the addition of the step merely constitutes the addition of a step that would be considered by one of skill in the art to be the inevitable concluding step to the series of steps preceding it. The skilled artisan would certainly understand that the highly designable stacks are represented in the computer as 3-dimensional backbone coordinates, and for comparison to known natural structures, the highly designable stacks are also represented specifically in terms of 3-dimensional center-of-mass and angular coordinates of the constituent secondary structural elements. Figure 3 of the instant application provides a schematic visual representation of the determined highly designable stacks, including the novel orthogonal array, and Table II presents binary sequences which have these structures as lowest energy folds. The Examiner is referred to the disclosure on page 23, lines 3-27 of the instant specification, which disclosure describes, inter alia, the meaning and import of Figure 3 and Table II.

IV. Rejections under 35 U.S.C. §112, Second Paragraph

The Examiner has leveled a number of rejections under 35 U.S.C. §112, second paragraph, making various assertions of indefiniteness of the claims.

Claim 1 is cited for reciting the term "known counterpart." In the first place, again, the meaning of "known" is clear from page 22, lines 17-22 of the specification, the passage cited by the Examiner in the new-matter rejection. Again, as would be appreciated by one of skill in the art, the terms "known" and "natural" can be used interchangeably in this context.

The Examiner further asserts that the term "known" does not appear to be a relative one, at the same time acknowledging that if a protein or a peptide configuration can be found in an available database, it would be considered "known." However, the Examiner asserts that one still would not understand what it is intended as a "counterpart" and that, apparently, even if one could understand what is meant by "known" (which one clearly can), one would not know what is meant by "known counterpart." However, what is meant by "counterpart" would also readily be understood by one of skill in the art. The term "known counterpart" conveys the intention that the comparison of the generated highly designable stacks be made to single, known protein domains as potential natural counterparts. A single protein domain constituting one domain of a multidomain protein would also be considered as a potential natural counterpart. A known counterpart in the present context is a structure that has the same fold, i.e., one having the same secondary structural elements and with the same three-dimensional orientation, as one generated by the instantly claimed method. This rejection must be withdrawn.

Claim 1 is also said to be indefinite because it is not clear what is intended by the "representing" step. The Examiner indicates that the term has been interpreted at present to mean "displaying," but requests clarification. Applicants hereby confirm that this is one way in

which representation might occur. As would be appreciated by one of skill in the art, however, backbone configurations can be represented in several ways, for example, in terms of three-dimensional coordinates or via graphical display. For example, the results could just as easily be represented in the computer as a file containing the coordinates and/or dihedral angles defining the three-dimensional structures of the identified folds.

Claim 1 has further been rejected for reciting the term "based on" in step (d). In practice, this step involves taking some fraction of the most highly designable stacks for consideration. In any event, step (d) has been amended by the deletion of the term and its replacement by language that the Examiner must acknowledge meets the criteria of the statute.

Claim 9 has been rejected for being indefinite as to whether the further recited limitation is meant to be an additional step or to be a replacement for step (b) of claim 1. The intention was that the further limitation be considered a part of step (b), and the claim has been amended along the lines suggested by the Examiner.

Claim 13 has been rejected as indefinite for reciting "applying a predetermined constraint" and "confirming that each said stack of the set does not exceed said predetermined constraint." In so doing, the Examiner has alleged a distinction between application of a constraint and comparison to a constraint. Claim 13 as amended recites neither "applying" nor "comparing" the constraint and fully addresses the Examiner's concerns in this regard and in connection with the context in which the constraint is to be employed. Support for the amendment can be found in the specification passage running from page 13, line 27 to page 14, line 4.

Claim 13 stands further rejected as indefinite for reciting the phrase "is discarded." This aspect of the claim has been amended as suggested by the Examiner so that it reads as an active part of the steps of the claimed method.

Claim 13 has further been rejected for alleged lack of antecedent in basis in connection with "each said stack of the set." The claim has further been amended to address this rejection.

Claim 14 has been rejected as indefinite for recitation of the phrase "connected helices." Although the Examiner has not leveled per se an antecedent-basis rejection, it is stated in the rejection that "no helices are recited in any parent claim...." The word "helices" has been replaced with language found literally in claim 1, and the rejection is moot. As is clearly disclosed in the specification and known in the art, helices are an example of secondary structural elements; the amendment of the claim is remedial and proper. The amendment is further supported by the specification on page 14, lines 4-6.

Claim 16 has been rejected as being indefinite as to what is meant by "a plurality of stacks are generated." The claim has been amended as the Examiner has suggested to recite the limitation as an active step in the claimed method.

Claim 16 has further been rejected for containing the phrase "based on." This rejection is along the lines of that leveled against the same language in step (d) of claim 1. The claim has been amended by deletion of the phrase and replacement with language that renders the rejection moot.

Claim 18 has been rejected for containing a phrase which clearly is inadvertently in error. The claim has been amended to correct the errors. The claim has also been amended to depend from a claim that provides antecedent basis for the term "plurality of stacks."

Similarly, claim 19 has been rejected on the basis of an inadvertent error. Again, the claim has been amended to correct the error.

Claim 21 has been rejected for lack of antecedent basis in connection with "said clustered stacks." The claim has been amended so that it depends from claim 20, and the rejection is moot.

Claim 22 has been rejected as being indefinite as to what is referred to by "said process." The claim has been amended to clarify that it is the elimination process that is intended, and this rejection is also moot.

Claim 22 has further been rejected for allegedly lacking antecedent basis with respect to the term "said list." This rejection is not warranted. Claim 21, from which 22 depends, recites that the clustered stacks are "sorted and listed." Thus, clearly, a list is generated according to the method of claim 21 and there is antecedent basis for the list recited in claim 22.

Claim 22 stands further rejected as being indefinite as to what is intended by the terms "are eliminated" and "is repeated." The claim has been further amended to make clear that these are intended to be active steps in the claimed method.

Claim 23 has been rejected as indefinite for failing "to recite any active method step or a clear (further) limitation of any step of claim 1." The claim has been amended to make clear that the "generating" step is an active one and is part of step (c) of claim 1. Although an antecedent-basis rejection per se has not been leveled, the Examiner has indicated that part of the alleged indefiniteness arises from the recitation in claim 23 of "amino acid sequences" when "sequences" are not recited in claim 1. Applicants wish to point out that, while the word "sequences" may not literally appear in claim 1, step (a) of the claim recites "amino acid secondary structural elements." It is a given, then, that these elements, whether they be alpha



helices or beta strands, must comprise sequences of amino acids. Therefore, there is sufficient antecedent basis, even if that basis is not literal.

Claim 23 stands further rejected for reciting the phrase "based on." This rejection is along the lines of that previously set forth for step (d) of claim 1 and for claim 16. The phrase has been deleted, and the rejection is moot. It should also be noted that although the complete phrase deleted is "based on binary sequences," it would be clear to one of skill in the art, both from his or her own knowledge and from the disclosure of the instant specification, that the sequences of claim 23 are in fact binary, consisting of "H" and "P" units.

Claim 24 has been rejected on several grounds as indefinite for recitation of the phrase "is reduced." In the first place, similarly to other claims herein, this claim has been amended to make clear that the intended additional limitation is an active step in the claimed method. It has further been amended to clarify that the reduction is intended to take place in step (c) of claim 1, i.e., is part of the evaluation-of-designability aspect of the claimed method. Support for this can be found in the specification from page 16, line 6 to the end of page 17.

The Examiner further holds that it is unclear what is meant by reducing a sequence to the hydrophobicities of its individual amino acids. Applicants wish to clarify that the reduced sequences are strings of real numbers connoting the relative hydrophobicities or polarities of the amino acids. This claim differs from claim 23 in that the sequences are not necessarily binary. In this case, the numbers span the spectrum from highly polar amino acids such as arginine or glutamic acid on one end to hydrophilic ("neutral polar") amino acids such as serine and threonine to, at the other end, hydrophobic amino acids such as leucine and phenylalanine.

Applicants also wish to point out that ample description of the concept of reduction is provided in the specification from page 16, line 12 to the end of page 17. It is noted that while

the phrase "reduction to hydrophobicities" has been deemed unclear as justification for leveling an indefiniteness rejection, it appears that the meaning of the phrase was adequately enough conveyed to the Examiner to enable her to make the assessment that Dahiyat teaches the concept and thus provides justification for leveling an anticipation rejection of claim 24 (see Section V below).

Claim 28 stands rejected as indefinite, the Examiner asserting that the claim "recites the phrase 'with said stack as the lowest energy state', which is nonsensical." In the first place, Applicants do not believe that this assessment is justified. Claim 28 clearly recites that a stack that accommodates a threshold number of amino acid sequences in the lowest energy state is considered to be a highly designable one. The Examiner further asserts that it is unclear what is intended by the phrase "larger than the average...." The claim clearly conveys that each stack has a certain number of sequences for which said stack is the lowest energy state. One takes the average of the number of such sequences for each stack, and any stack which has a number of sequences greater than the average is considered to be highly designable. It is thus clear that what is meant in claim 28 is that stacks with the property described in claim 28 are defined to be highly designable.

The Examiner further asserts that the claim is unclear with respect to the phrase "is identified." As in other claims, this language has been amended to clarify that what is intended is an active step in the claimed method.

The Examiner has deemed claim 28 to be so unclear as to be "unsearchable" and has not examined the claim with regard to the prior art. Applicants do not believe that this characterization of the claim was warranted in the first place, and it certainly cannot stand in the wake of the explanation above and the amendments herein to the claim. Withdrawal of the

rejection and consideration of the claim in any further prior art considerations made by the Examiner are respectfully requested.

V. Rejection under 35 U.S.C. §102

Claims 1-7, 15, 20 and 23-25 remain rejected under 35 U.S.C. §102(b) as anticipated by the Science article of Dahiyat et al. Again, Applicants disagree with this assessment.

The Examiner has misinterpreted the cited passage found on page 86, column 2 of Dahiyat. Contrary to the Examiner's assessment, Dahiyat's statement that the  $\beta\beta\alpha$  fold is "different" does not mean "different from a 'known' configuration." Clearly, the  $\beta\beta\alpha$  fold was known—it is taken from a known zinc finger. Dahiyat is merely stating that the fold "is different from those [already] used [by Dahiyat and coworkers] to develop the methodology...." Similarly, the Dahiyat reference to "a new motif" does not mean the motif is novel; Dahiyat simply refers to the successful transfer of the disclosed algorithm to a motif not previously used [by Dahiyat and coworkers].

What Dahiyat is referring to in the passage cited by the Examiner is made manifestly clear by Dahiyat's own words on page 82, third column, end of the last complete paragraph: "The  $\beta\beta\alpha$  motif was not used in any of our prior work to develop the design methodology and therefore provides a test of the algorithm's generality." Clearly, Dahiyat was not interested in applying his algorithm to unknown, undetermined configurations. Rather, Dahiyat was interested in showing that his algorithm, which was trained on a particular set of known structures, could be used on another known structure (the  $\beta\beta\alpha$  fold) that was not in the training set. If the  $\beta\beta\alpha$  fold had been used in developing the algorithm, then even successful application of the algorithm to the  $\beta\beta\alpha$  fold would not prove the algorithm's general utility—it might only apply to structures in the training set.

It cannot be emphasized enough that Dahiyat does not in fact teach “a method of identifying protein backbone configurations which are different from those of a known protein (i.e., a ‘novel’ configuration). . . .” Accordingly, the Examiner’s fundamental basis for leveling the anticipation rejection is without merit and cannot stand. Furthermore, whether or not Dahiyat can be said to teach the specific limitation of claims 6, 7, 15, 20 and 23-25 can have no effect on the analysis of patentability, since the application of those limitations is to the method of Dahiyat, which clearly is not, and cannot be, the instantly claimed method. Applicants note that the Examiner rejected claim 24 as indefinite on the allegation that the concept of “reduction to hydrophobicities” is unclear, but at the same time seems to have had a clear enough idea of what is meant by the phrase to assert that claim 24 is anticipated by a particular teaching of Dahiyat. Whether or not it can be said that Dahiyat teaches or suggests this particular concept, it does not teach the fundamental method that is the present invention.

The Examiner goes on to assert that Applicants’ prior arguments are not persuasive because the present claims “do not recite any step of generating any novel backbone configurations.” Applicants do not understand the basis for making this assertion. It is noted that the claims previously did literally recite “novel...configuration” but the claim was amended in response to a prior “new matter” rejection leveled by the Examiner. Now the Examiner is attempting to penalize Applicants for their bona fide response to a previous rejection. Furthermore, it must be pointed out that although claim 1 may not be directed literally to “novel...configurations,” it is inarguably directed to “configurations which are novel in the spatial arrangement and/or connectivity of their secondary structural elements.” Thus, the Examiner’s assertion that the limitations said to be lacking from Dahiyat are not to be found in

the present claims is without merit. Furthermore, again, Dahiyat's algorithm is not for use in the identification of new, previously unknown configurations.

In rebutting Applicants' previous arguments, the Examiner again refers to the "known counterpart" issue, implying that the indefiniteness of the term means that Applicants' assertion about the distinction between the instantly claimed method and that of Dahiyat cannot be found persuasive. However, as set forth above, it can in fact be understood by one of skill in the art from the disclosure in the specification what is meant by the term. It cannot be emphasized enough that the Examiner's assessment that "DAHIYAT does teach identifying a combination of secondary structural elements (i.e. a set of stacks) which is different from other, known, structures and is a new 'novel' motif..." is in error. Dahiyat does not teach a method for generating a configuration having "no known counterpart."

Anticipation requires that each and every element be identically disclosed in a single reference. The Examiner's burden in this regard has not been carried. The Dahiyat passages cited by the Examiner in paragraphs 21-26 of the previous Office Action are all ultimately tied in with identification of alternative amino acid sequences to be inserted into a prespecified, known backbone configuration. This is not the present invention as defined by the steps of claim 1. Furthermore, any specific techniques and/or parameters disclosed in these Dahiyat passages and used as a basis for rejection of dependent claims in the present application are applied to this same Dahiyat framework of working with a prespecified, known backbone configuration.

#### VI. Rejection under 35 U.S.C. §103

The rejection of claims 1-7, 9-11, 15, 16, 20 and 23-25 as obvious over the same Dahiyat article in view of U.S. Patent No. 6,403,312 to Dahiyat et al. has also been maintained. Again, Applicants emphatically disagree with this assessment.

The Examiner has found Applicants' previous arguments unpersuasive because they "are directed to limitations not recited in the claims. The instant claims do not recite identification or [sic] 'previously unknown, realizable backbone configurations' nor 'means for designing protein backbone configurations ....'" The Examiner apparently feels that Applicants should have used the identical words in their arguments that are found in the claims; however, the fact that this was not done in no way lessens the effectiveness of said arguments. Furthermore, U.S. patent practice does not even require the use in the claims of exactly the language that may originally have been used. Although the instant claims do not literally recite the specific phrases invoked by the Examiner, they do recite "identifying protein backbone configurations which are novel in the spatial arrangement and/or connectivity of their secondary structural elements" and that the identified configurations comprise stacks of high designability. The identification of these configurations must be seen as constituting design of said configurations in the context of the present invention.

The primary reference in this obviousness rejection is the same Dahiyat article used as the basis for the anticipation rejection and discussed above. Again, the Examiner's assessment of what the primary reference teaches is in error, and the primary reference is ineffective as prior art. The teaching of a method for identifying novel protein backbone configurations, erroneously attributed to the primary reference and necessary for the effectiveness of the obviousness rejection, cannot be found in the secondary reference either. Neither the alleged teaching of the secondary reference of the use of a protein library nor the specific teaching of the use of a conjugate gradient method, also attributed by the Examiner to the secondary reference, furnishes the teaching that the Dahiyat article fails to provide. Accordingly, the Examiner has failed to meet the burden of establishing a prima facie case of obviousness. More particularly, the

Examiner has failed to establish that the combination of the cited references would reasonably lead one of ordinary skill in the art to the claimed invention. Thus, regardless of considerations of motivation to combine what teachings are truly available to the skilled artisan via the two references, the rejection cannot stand and should be withdrawn.

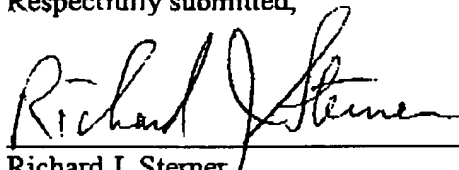
#### VII. Conclusion

The amendments to the claims have addressed the new matter and enablement issues raised by the Examiner. Furthermore, the combination of claim amendments and arguments presented above make clear the patentable distinction between the claimed invention and the teachings of the cited references. Reconsideration and allowance of the application with pending claims 1-25 and 28 are respectfully requested. Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

No additional fees should be due in connection with this communication. However, should it be determined that an additional fee is due for any reason, the Commissioner is hereby authorized to charge it to Deposit Account No. 23-1703.

Dated: August 28, 2006

Respectfully submitted,



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